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Changes in Diastolic Properties of the Regional Myocardium During Pacing-Induced Ischemia in Human Subjects

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Mechanisms related to alterations in the diastolic properties of the left ventricle during angina were studied in seven patients with coronary artery disease. Single plane left ventriculograms were obtained using a high fidelity micromanometer-tipped catheter in both the resting state and immediately after rapid cardiac pacing. In all patients, typical anginal pain developed with pacing stress. After atrial pacing, the left ventricular end-diastolic pressure increased from 10 ± 3 to 21 ± 7 mm Hg (± standard deviation) ($p < 0.005$) regardless of the changes in the end-diastolic volume. The ejection fraction was reduced from 59 ± 10 to 48 ± 13% ($p < 0.05$). The diastolic pressure-volume curves shifted upward in post-pacing beats in four patients, while in three the curves shifted more to the right.

The regional myocardial function was expressed in quantitative terms by a radial coordinate system with the origin at the center of gravity of the end-diastolic silhouette. Two representative radial grids for normal and ischemic segments were selected. In the normal segment, the end-diastolic length was augmented by 15% ($p < 0.005$) and was associated with a 24% increase in stroke excursion with pacing stress ($p < 0.05$). The increase in diastolic pressure was accompanied by comparable increases in end-diastolic length, and the diastolic pressure-length relation moved up to the higher portion of the single curve. In the ischemic segment, the end-diastolic length remained unchanged in the post-pacing beat, but segment shortening was significantly reduced. The diastolic pressure was higher at any given length and the pressure-length curve clearly shifted upward, indicating regional alteration of the diastolic property of the ischemic myocardium.

Thus, the net global changes in the ventricular chamber compliance are determined by the complex interaction of changes in pressure-length relation of the regional myocardium.

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Left ventricular end-diastolic pressure increases characteristically during attacks of angina in patients with coronary artery disease (1,2). An impaired contractile performance with larger diastolic volume (3) or altered diastolic properties (4–10) with a change in the pressure-volume relation would be responsible for this elevation of end-diastolic pressure. The observed shift of left ventricular pressure-volume relations associated with pacing-induced angina has been attributed to the persistent diastolic interaction of contractile elements within the left ventricular myocardium, possibly related to both incomplete myocardial relaxation and altered diastolic tone during ischemia (11).

However, many investigators have studied the effects of hypoxia or anoxia on the passive elastic properties of the myocardium using isolated papillary muscle (12) or the isovolumic canine heart (13,14) and found that ischemia did not immediately affect ventricular diastolic properties. The elevation in left ventricular end-diastolic pressure during ischemia in otherwise normal canine myocardium has been considered to be mediated by a decrease in systolic performance of the heart rather than by an alteration of the pressure-volume relation (3). The pericardium itself also affects the left ventricular diastolic pressure-volume relation by coupling left and right ventricular pressure (15) and inducing interaction of right ventricular filling pressure and intrapericardial pressure (12,16). On the other hand, in the presence of regional myocardial ischemia, global function

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of the left ventricle alone can be misleading, and an analysis of the regional myocardial function is necessitated.

Description and quantitation of this regional myocardial function have been provided in the experimental setting (17–19); however, there are methodologic limitations in clinical assessments. We developed a computer-aided means of processing cineventriculographic studies for the analysis of contraction and relaxation of specific segments of the left ventricular myocardium (20–22).

In the present study, we constructed diastolic pressure-length curves of the regional myocardium by plotting instantaneous pressure against radial length. The method allowed, for the first time, the simultaneous characterization of the distensibility of the regional myocardium of the left ventricle and an analysis of the effect of pacing-induced ischemia on regional diastolic properties in patients with coronary artery disease.

Methods

Study patients. The study was performed in seven patients with coronary artery disease and angina on effort. Those with global ischemia due to multivessel disease were excluded. All the patients were in normal sinus rhythm and all medications were withheld for 12 hours before the procedure. Informed consent was obtained from each patient and there were no complications.

Catheterization procedure. Cardiac catheterization was performed using the left brachial approach with the patient in a fasting state and after premedication with 5 mg of oral diazepam. After conventional diagnostic right and left heart catheterization, coronary arteriography was performed using the Sones technique. A pacing catheter was positioned in the right atrium. A high fidelity micromanometer-tipped catheter (Mikro-Tip, Millar Instruments) was then introduced into the left ventricle through the left brachial artery, which allowed simultaneous high fidelity pressure measurement during angiography. After it was confirmed that ventricular pressure had returned to baseline after coronary arteriography, left ventricular cineangiography was performed in the 30° right anterior oblique projection using a Philips 9 inch (22.9 cm) image intensification system. Left ventricular opacification was achieved by injecting 25 to 40 ml of radiopaque contrast medium (80% Angiografin) through a Millar angiographic catheter at a rate of 12 ml/s. Films were exposed at a rate of 60 frames/s with an Ari 35 mm cine camera.

Pacing protocol. During each cineangiographic study, high fidelity left ventricular pressure, electrocardiogram, cineangiographic frame markers and an injection marker were simultaneously recorded. Two lead markers were placed on the image intensifier as fixed references for superimposition of the images. An adequate recovery time was allowed for left ventricular pressure to return to baseline. The atrial pacing was initiated at a rate of 90 beats/min and was increased in increments of 30 beats/min every 2 minutes. In patients in whom atrioventricular block developed during atrial pacing, right ventricular pacing was substituted. Pacing was stopped with the occurrence of chest pain. If well tolerated, pacing was continued at a rate of 150 beats/min for 6 minutes. The second angiogram was obtained immediately after the cessation of pacing in the same manner as in the control state (20).

Analysis of Data

Boundary detection. The method of automatic processing of cineangiography has been described elsewhere (20,22). Briefly, the left ventricular images on cine film were transferred to a computer through a flying spot scanner and were stored on a magnetic disk. Each digitized image consisted of 128 × 128 pixels with gray levels of 256 values. A gradient image was then obtained by spatial differentiation of gray levels. Assuming that the abrupt change of the gray levels occurred at the boundary of the ventricular silhouette, the points with the maximal gradient value were traced to delineate the ventricular boundary.

For the algorithm for each computer tracing of edge points, two weight coefficients were introduced to multiply the corresponding derivative value. One is denoted as the directional weight coefficient, which enables avoidance of an abrupt change in direction of edge tracing. The other is the coefficient to define the depth of search when information of several remote points was considered. The additional global guidance was obtained from the preceding frame. All these procedures closely imitate visual detection of a boundary by the human eye (20).

Analysis of global left ventricular function. The left ventricular volumes (V) were calculated by a modification of the formula of Kennedy et al. (23):

$$V = 0.687 \times C^3 \times A^2/L + 1.9 \text{ ml},$$

where A is the area of the ventricle calculated from the amount of pixels surrounded by the left ventricular boundary, L is the longest measured length between the midpoint of the aortic valve and the apex and C is the linear correction factor for the magnification of a unit of length (1 pixel), which was derived from a comparison with the known area of the filmed 1 cm^2 grid, placed in parallel to the tube at the position of the heart.

The calculated volume of each frame was synchronized to corresponding pressure by a simultaneously recorded exposure marker throughout diastole to obtain the diastolic pressure-volume curve. Comparison was made between control diastolic pressure-volume curves and those obtained in the post-pacing period.

Analysis of regional left ventricular function. Sequential ventricular silhouettes were superimposed on the end-diastolic frame throughout the cardiac cycle by using two external reference markers. In each superimposed ven-

tricular image, 128 radial grids were drawn from the center of gravity of the end-diastolic silhouette to the endocardial margin. Measurement of the length of each grid line throughout the cardiac cycles made it possible to analyze contraction and relaxation of specific segments of the left ventricular myocardium (20).

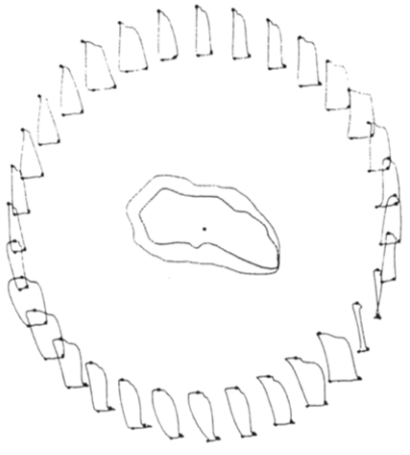
The length of each radial grid plotted against time was handled in the same way as an overall volume-time curve to construct the diastolic pressure-length curve. The pressure-length loops were originally generated for 128 radial grids but were reduced to every fourth grid, resulting in a display of 32 loops over the entire ventricular circumference (Fig. 1). To analyze the effect of pacing stress on the ischemic myocardium, the potentially ischemic section corresponding to the known coronary lesions, in which active shortening was preserved at rest, was selected and the response to cardiac pacing was compared with that of the normal section perfused with intact coronary arteries (Fig. 2). In the patients with overt myocardial infarction, the section that included the central ischemic region was excluded, because neither dyskinetic nor akinetic motion of the definite infarction area was modified substantially by pacing stress.

Statistics. All data were expressed as mean ± standard deviation. Statistical comparisons were made by a paired *t* test.

Results

Table 1 summarizes data obtained from the seven patients. In all, there was a significant stenosis or obstruction in one of the major branches of the coronary artery on angiography and typical anginal pain developed during pacing tachycardia.

Figure 1. Representative pressure-length loops constructed by relating the length of each radial grid to instantaneous left ventricular pressure throughout the cardiac cycle. The loops were originally generated for 128 radial grids, but were reduced to every fourth grid, resulting in a display of 32 loops over the entire ventricular circumference. The center of gravity of the left ventricular end-diastolic frame is indicated by the **dot**.



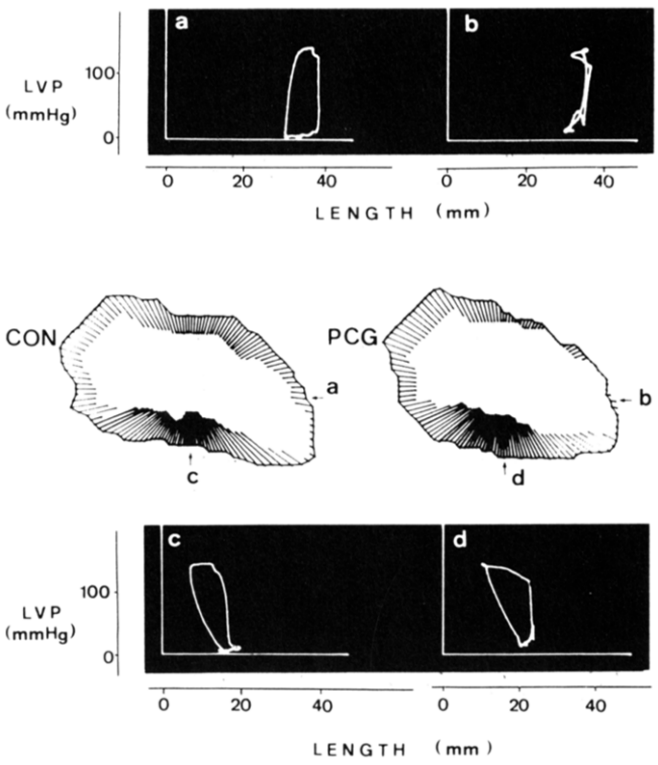


Figure 2. Comparison of pressure-length loops at resting state (control [CON]) (**grid a** and **grid c**) and after rapid cardiac pacing (PCG) (**grid b** and **grid d**) for the representative two segments in the normal (**lower panel**) and ischemic (**upper panel**) areas. Pacing stress caused a remarkable increase in the left ventricular diastolic pressure and striking deformation of the loop configuration. LVP = left ventricular pressure.

Hemodynamic findings and global ventricular function. In post-pacing beats, heart rate did not change significantly. Left ventricular peak systolic pressure remained unchanged, while end-diastolic pressure increased from 10 ± 3 to 21 ± 7 mm Hg ($p < 0.005$). Although there were no consistent changes in left ventricular end-diastolic volume, end-systolic volume was uniformly augmented from 39 ± 17 to 55 ± 24 ml ($p < 0.03$). Stroke volume was unaltered (53 ± 12 versus 48 ± 13 ml), but ejection fraction was reduced from 59 ± 10 to 48 ± 13% ($p < 0.05$). Rapid cardiac pacing elicited short-term reversible abnormalities in segmental function on the post-pacing ventriculogram compared with the control ventriculogram.

Regional myocardial function during angina. To evaluate the heterogeneity of regional myocardial function in response to pacing stress, we selected two representative radial grids for normal and ischemic regions. The former was the section that showed the compensatory augmentation of shortening in the post-pacing beat. The latter was the section in which active contraction was maintained at rest, but in which the coronary reserve was critically limited and

Table 1. Summary of Data in Seven Patients With Coronary Artery Disease and Angina on Effort

Case	Age (yr) & Sex		Normal Segment (mm) EDL	ESL	ΔL	Ischemic Segment (mm) EDL	ESL	ΔL	HR (beats/min)	LVP (mm Hg)	EDP (mm Hg)	EDV (ml)	ESV (ml)	SV (ml)	EF (%)	CAG Findings
1	70M	C	19.7	9.3	10.4	36.8	29.9	6.9	60	139	12	75	30	45	60	Left main 90%
		P	21.7	9.5	11.2	32.9	28.8	4.1	53	135	30	71	32	39	54	stenosis
2	54M	C	19.0	8.1	10.9	31.1	27.0	4.1	61	148	9	103	38	65	63	LAD 99%
		P	23.2	8.5	14.7	30.7	28.7	2.0	55	168	17	112	46	66	58	stenosis
3	47M	C	29.9	24.6	5.3	38.2	37.0	1.2	58	120	15	112	42	70	62	RCA 99%
		P	30.4	23.7	6.7	36.9	36.3	0.6	65	113	22	106	47	61	56	stenosis
4	68F	C	32.8	23.7	9.1	28.9	22.7	6.2	63	124	6	130	68	62	48	LAD distal 100%
		P	37.5	26.8	10.7	30.7	27.2	3.5	65	130	11	140	86	54	39	obstruction
5	71F	C	25.0	12.0	13.0	18.7	9.7	9.0	85	148	7	58	17	41	71	RCA 99%
		P	30.3	11.0	19.3	19.4	14.2	5.2	79	165	16	77	27	50	65	stenosis
6	70F	C	22.1	12.4	9.7	29.5	12.9	16.6	90	143	11	75	24	51	68	LAD 99%
		P	25.5	14.8	10.7	28.8	21.0	7.8	99	146	27	86	57	29	33	stenosis
7	74M	C	24.8	11.5	13.3	37.0	27.1	9.9	61	143	8	92	52	40	43	LAD 100%
		P	31.2	16.5	14.7	40.5	38.2	2.3	55	138	27	128	88	40	31	obstruction
Mean		C	24.8	14.5	10.2	31.5	23.8	7.7	68	138	10	92	39	53	59	
± SD			5.1	6.6	2.7	6.8	9.6	4.9	13	11	3	25	17	12	10	
		P	28.5	15.8	12.6	31.4	27.8	3.6	67	142	21	103	55	48	48	
			5.5	7.1	4.0	6.7	8.3	2.4	17	19	7	26	24	13	13	
p Value			<0.005	NS	<0.05	NS	<0.05	<0.03	NS	NS	<0.005	NS	<0.03	NS	<0.05	

C = control; CAG = coronary arteriography; ΔL = segment shortening; EDL = end-diastolic length; EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; ESL = end-systolic length; ESV = end-systolic volume; F = female; HR = heart rate; LAD = left anterior descending artery; LVP = left ventricular pressure; M = male; NS = not significant; P = post-pacing; p = statistically significant difference before and after pacing stress; RCA = right coronary artery; SD = standard deviation; SV = stroke volume.

pacing stress temporarily provoked a significant deterioration of regional shortening (Fig. 2).

In the ischemic area, active shortening was abolished from the beginning and was not modified by the pacing stress. Therefore, the potentially ischemic area surrounding the central ischemic area was selected for the present analysis of regional function of the ischemic myocardium.

In the normal segment, the end-diastolic length was augmented by 15% from the control value of 24.8 ± 5.1 mm ($p < 0.005$) and was associated with a 24% increase in stroke excursion ($p < 0.05$). *In the ischemic segment,* the end-diastolic length remained unchanged in the post-pacing beat, and the stroke excursion was decreased by 53% ($p < 0.03$).

Diastolic pressure-volume relation. Diastolic pressure-volume curves before and after rapid cardiac pacing in all seven patients are shown in Figure 3. The pressure-volume curves shifted upward remarkably in the post-pacing beat in four patients (Cases 1 to 4), while the curve shifted more to the right associated with this upward shift in three patients (Cases 5 to 7).

Diastolic pressure-length relation of the regional myocardium. Plots of left ventricular pressure against normal and ischemic segment length throughout passive ventricular filling are shown in Figure 4. In all cases, the increase in diastolic pressure was accompanied by the comparable increases in end-diastolic length in the normal segment. Thus, the normal segment appeared to be operating at the higher portion on the single pressure-length curve. In the ischemic segment, pressure was higher at any given segment length in the post-pacing beat and the pressure-length curves clearly shifted upward, indicating regional alteration of the diastolic property of the ischemic myocardium. Accordingly, the observed global shifts of the pressure-volume relation are net results determined by the interaction of regional diastolic properties of the normal and ischemic myocardium.

Discussion

Analysis of regional myocardial function. Impairment of ventricular function in ischemic heart disease depends on the mechanical dysfunction of different regions of the left ventricle, and analysis of a single pressure-volume curve does not adequately define the diastolic property of the left ventricular myocardium during ischemia. In experimental settings, several methods have been described for quantitative analysis of regional myocardial function (17–19), whereas in clinical settings, there remain significant methodologic limitations to the expression of such regional wall motion in more quantitative terms.

For the analysis of localized myocardial dysfunction in patients with coronary artery disease, we developed a computer-assisted image processing system of cineventriculography in which segmental wall motion was expressed as

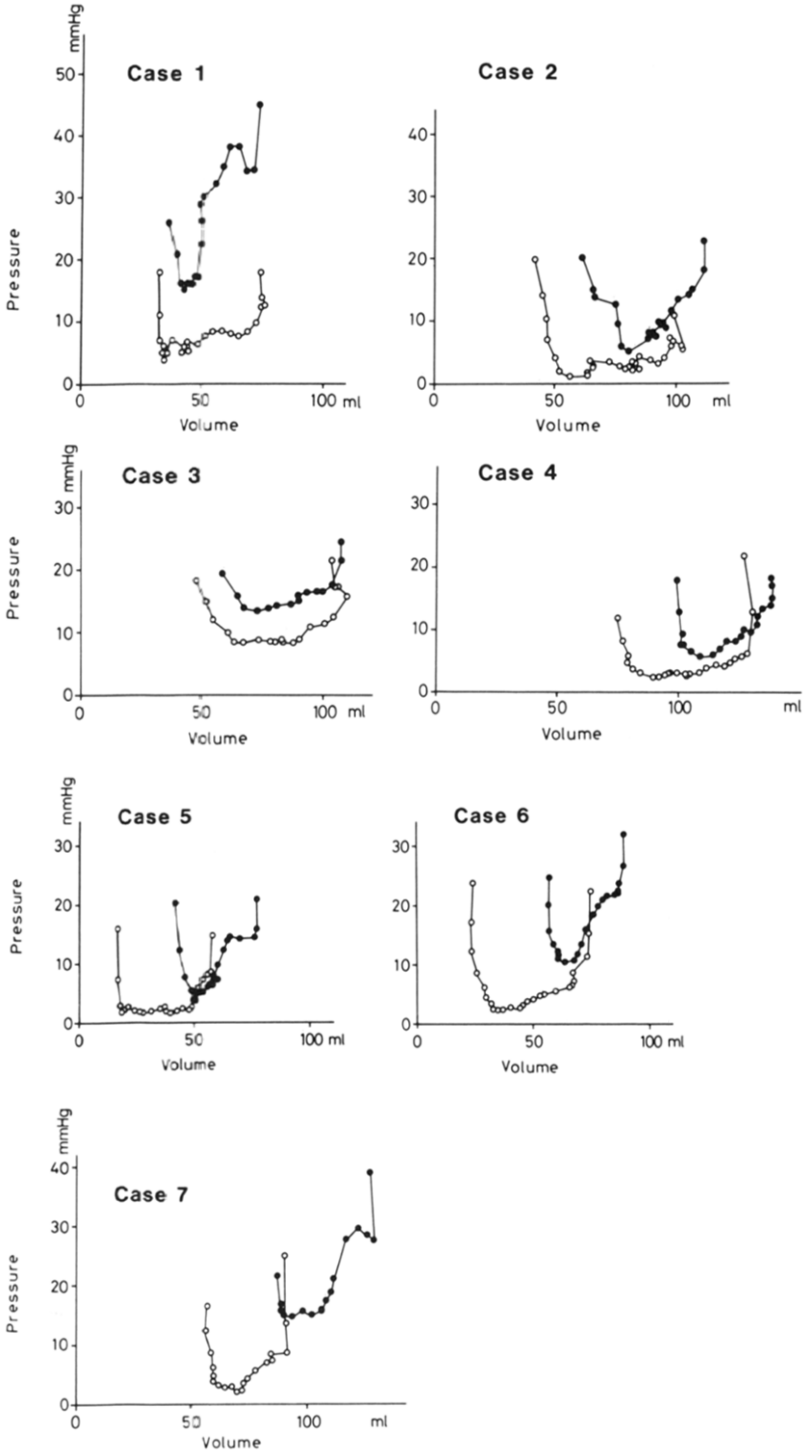


Figure 3. Left ventricular diastolic pressure-volume relations before (**open circle**) and after (**closed circle**) rapid cardiac pacing in seven patients with coronary artery disease. The curve shifted directly upward in four patients (Cases 1 to 4) and upward and more to the right in three patients (Cases 5 to 7) in the post-pacing beat compared with the control.

changes of the length of the radial grids drawn from the center of the gravity of the end-diastolic silhouette to the endocardial margin (20–22). Time-length plots of a given radial grid allowed for characterization of contraction and relaxation of the specific region of the left ventricular wall in accurate temporal and spatial relations.

In the present study, the length of each radial grid was related to corresponding left ventricular pressure throughout diastole. This method has enabled, for the first time, a simultaneous construction of the diastolic pressure-length curves in several portions of the left ventricular wall in clinical settings, and regional changes in diastolic properties induced by pacing tachycardia in patients with severe coronary artery disease were compared.

Pressure-volume relation. When global left ventricular compliance was analyzed by the diastolic pressure-volume

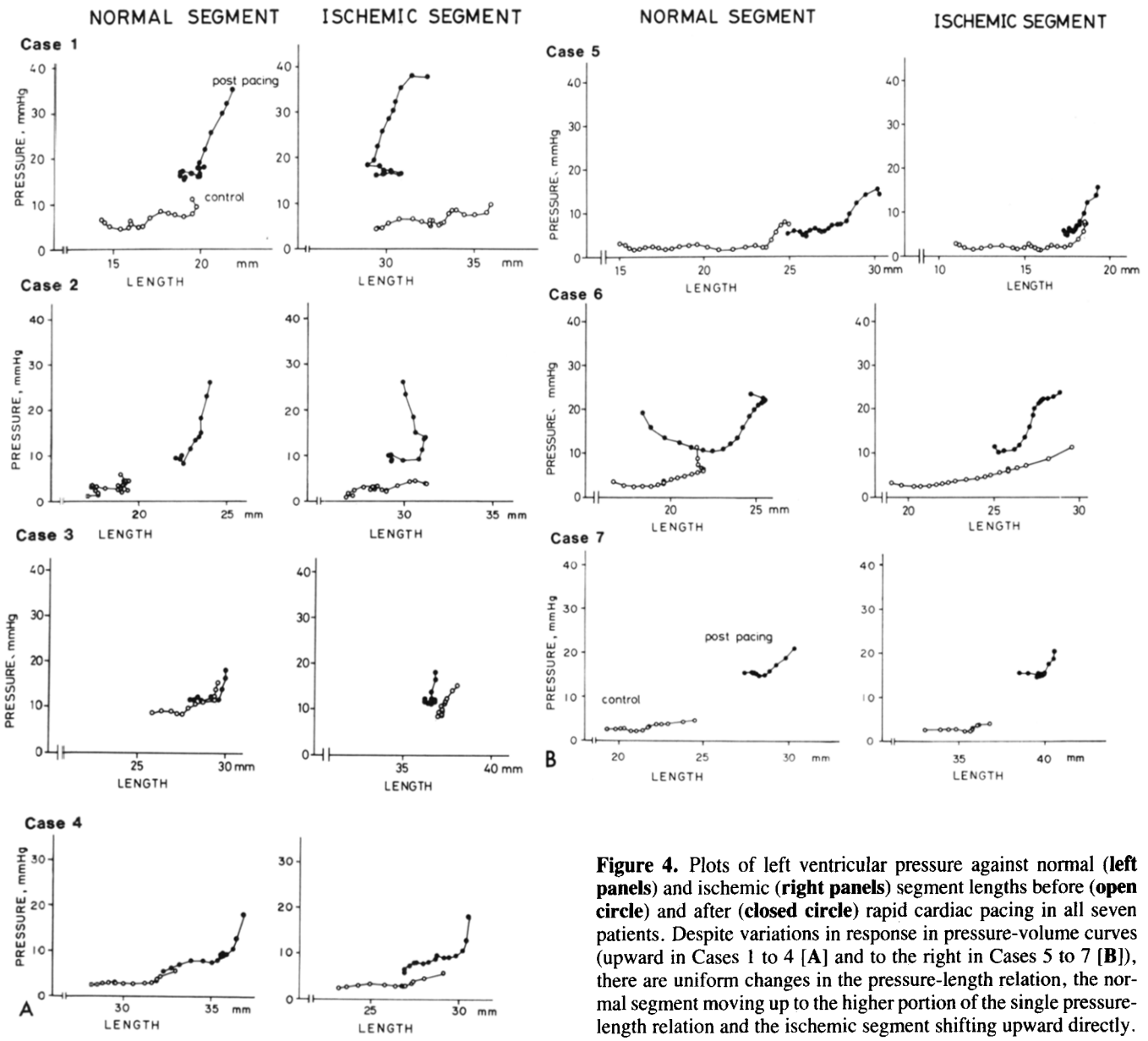


Figure 4. Plots of left ventricular pressure against normal (**left panels**) and ischemic (**right panels**) segment lengths before (**open circle**) and after (**closed circle**) rapid cardiac pacing in all seven patients. Despite variations in response in pressure-volume curves (upward in Cases 1 to 4 [**A**] and to the right in Cases 5 to 7 [**B**]), there are uniform changes in the pressure-length relation, the normal segment moving up to the higher portion of the single pressure-length relation and the ischemic segment shifting upward directly.

relation in these patients, we observed two responses. In four patients, left ventricular end-diastolic pressure increased out of proportion to changes in end-diastolic volume, with the left ventricular diastolic pressure-volume curve being shifted upward; in the remaining three patients, the increased end-diastolic pressure during ischemia was accompanied by an increase in left ventricular end-diastolic volume. These observations emphasize again the controversy concerning the factor more responsible for the increased end-diastolic pressure during angina: altered left ventricular diastolic properties with reduced compliance or transient left ventricular failure.

Pressure-length relation of the regional myocardium. In an analysis of the regional nature of responses, the displacement of the segmental diastolic pressure-length relation during pacing-induced ischemia was remarkably consistent depending on the ischemic status of the respective segment. We observed an upward shift of the segmental pressure-length relation in the ischemic region during angina. However, in the control region, the elevation of end-diastolic pressure was accompanied by a comparable increase in end-diastolic length and the segment appeared to have moved up on the single pressure-length curve to the higher and steeper portion.

When the coronary artery is suddenly occluded in the dog, the end-diastolic length increases more in the ischemic segment than it does in the normal segment. The ischemic sarcomeres are actually longer than control sarcomeres, and this overstretch is considered to be due in part to disengagement and rupture of the actin filaments (24). The in-

crease in end-diastolic length of marginally ischemic tissue during coronary occlusion is intermediate between that of the control and ischemic segments (17,18). The shortening of the marginal segment decreases despite the maximal use of the Frank-Starling mechanism. Thus, the more ischemic the tissue, the greater is the limitation of the preload reserve.

Altered diastolic properties in the ischemic myocardium. In our study, the curve of the ischemic segment initially shifted to the right either without a change in slope, suggesting an increased compliance (25), or with a steeper slope, indicating a reduced compliance (17). Théroux et al. (26) reported that late after myocardial infarction, the slope of this relation increased in association with a decrease in the end-diastolic length in the marginal and the ischemic segments but not in the control segment. These changes in the ischemic and marginal segments appeared to be related to tissue loss in the subendocardial region and to scar formation.

According to these experimental data, it is postulated that an additional acute ischemic insult during angina in patients with long-standing coronary artery disease will result in a less marked change in diastolic length in the ischemic region than in the normal region. Using a combined echocardiographic and hemodynamic technique, Bourdillon et al. (27) also demonstrated an upward shift in the left ventricular pressure-posterior wall thickness relation during pacing-induced angina in patients with severe coronary artery disease, though their method precluded study of more than one area. They assessed the extent of regional myocardial stiffness from the simultaneously obtained data on thickness and pressure, and demonstrated that a mathematically derived radial stiffness increased during angina induced by pacing tachycardia. The present observation of the upward shift in the diastolic pressure-length plots of the ischemic segments is consistent with these data of an altered distensibility in the regional myocardium.

Mechanism of changes in diastolic stiffness. It has been postulated that increased cytosolic calcium ion concentration and a low energy availability of the hypoxic muscle result in a reversible form of contracture caused by incomplete relaxation of the contractile elements throughout diastole and are responsible for increased stiffness of the ischemic myocardium (9). A prolongation of tension duration due to significant incomplete relaxation has been observed during the period of recovery from ischemia in isolated papillary muscle and isovolumically contracting canine hearts (28–30). These changes were related to the parallel prolongation of the plateau of the cardiac action potential (29). However, changes in the left ventricular diastolic property are already apparent during pacing tachycardia in which the duration of tension and action potential is shortened. Accordingly, the prolongation of contractile activity cannot be a major cause of a shift of the diastolic pressure-length curve in the ischemic myocardium.

It is generally agreed that some residual cross bridges within the contractile units may remain throughout diastole, resulting in persistent interaction among contractile elements (31). An increased cellular calcium concentration surrounding the contractile proteins and decreased availability of adenosin triphosphate for actin-myosin cross bridge dissociation could cause diastolic interaction of the contractile element and reversible form of contracture. Prevention of an increase in the pressure-volume relation of the rabbit heart during ischemia by the calcium antagonist nifedipine (32) offers support for this concept.

Diastolic properties of the normal myocardium during angina. In the normal area, a progressive increase in diastolic subendocardial segment length associated with enhanced shortening has been observed during healing after myocardial infarction (26,33). This change has been attributed to the later development of hypertrophy, much in the same manner as in the case of the long-term volume-overloaded ventricle, in which sarcomeres are added in series with no further operation of the Frank-Starling mechanism during progressive dilation of the ventricular cavity (26,33). Since preload reserve is nonlimiting relative to left ventricular function in the normal segment, additional ischemic insult probably causes further stretch of the segment associated with a higher diastolic pressure.

Our technique enables an analysis of the regional nature of the responses in the diastolic property during angina induced by pacing tachycardia. The complex interaction of changes in the myocardial mechanical properties of the different regions of the ventricle appears to be responsible for the net global changes in the ventricular chamber compliance.

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